Themed Issue: Intellectual Property Law and the Pharmaceutical Sciences
Guest Editors - Marilyn N. Martinez and Srikumaran K. Melethil

The Influence of Market Exclusivity on Drug Availability and Medical Innovations

Received: January 29, 2007; Final Revision Received: July 3, 2007; Accepted: July 11, 2007; Published: August 3, 2007

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Abstract

The interpretation and application of intellectual property laws is enormously complex in the pharmaceutical industry, with companies needing to obtain multiple patents to fully protect their innovations. While patents provide important incentives for biomedical innovation and economic growth, concern has been expressed over the growing number of patents, the granting of patents on basic research tools (eg, genetically engineered animals), and the possibility that these legal protections may ultimately inhibit scientific advancement.

Keywords: Intellectual property, FDA, patents, Hatch-Waxman, market exclusivity, orphan drug exclusivity, pediatric exclusivity, patent term restoration, generic drugs, ANDA

Introduction

Some of the world's best-known stories focus on characters who have awoken after many years and find themselves in a world that is at once familiar and alien. From Washington Irving's Rip Van Winkle to Mike Myers' Austin Powers, these characters experience jarring juxtapositions of yesterday and today. Nowhere in nonfiction has this been more evident than in pharmaceutical science. A pharmaceutical researcher who fell asleep in 1985 and awakened in 2005 would be stunned that infectious disease specialists were treating HIV infection as a manageable chronic illness; that endocrinologists treating type II diabetes mellitus had more than diet, sulfonylureas, and insulin to choose from; and that psychiatrists treating depression could select from a wide variety of medications with low side-effect profiles. Over the past 100 years, pharmaceutical research has helped transform health care, contributing substantially to an increase of over 30 years in life expectancy (from 47.3 years in 1900 to 77.5 years in 2003).[1] Yet we take these amazing advances for granted, assuming that better treatments for illnesses—new and old, exotic and mundane—are around every corner.

We live in exciting times in pharmaceutical science. Advances in basic sciences are allowing new products to reach patients rapidly. However, bringing a new drug to market today involves not only knowledge of molecular biology, chemistry, physiology, and medicine[2] but also a thorough understanding of economics, marketing, politics, and law (tax, regulatory, and Constitutional). New drug development is also very risky. For every 1 drug that reaches the market, ~5000 to 10 000 compounds are tested in preclinical trials, ~250 drugs are tested in preclinical animal trials, and ~5 drugs are tested in full-scale human clinical trials. Only 1 in 5 drugs entering clinical trials will gain US Food and Drug Administration (FDA) approval.[3]

This article explores the various forces bearing on the development of new drugs in the United States today. The article focuses on intellectual property (IP) law—specifically patents—and the intersection of IP law and federal regulations administered by the FDA.

Overview of US Patent Law

Article I, section 8, clause 8, of the US Constitution grants to Congress the authority to "promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries."[4] The founders realized the importance of recognizing an inventor's ownership interest in an invention. Such recognition provides an incentive for innovation, stability, and predictability of ownership, and, most importantly, a reason to share inventions with the public. The balance between private rights and public interest, as well as between innovation and access (or affordability), is at the heart of the present controversy surrounding IP laws and pharmaceutical products.

Patents exist to provide a limited property right in novel, useful things. They vest in their owners the right to exclude others from making, using, or selling (among other activities) the patented material for a limited time.[5] In exchange for that right, the patent owner must surrender to the public

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a detailed description of the new and useful thing sufficient to allow a knowledgeable person (one of ordinary skill in the art) to make or use the invention. The rationale for creating this right is to spur research and development by providing exclusive incentives to innovators. The right is limited both by the requirement that the patentee put the public in possession of his or her ideas and by the time-limited nature of the right.

It is impossible to understand the role of IP rights, as they exist in the United States today, without understanding the current regulatory environment. Below, we review the complex legislation that attempted to modernize and equalize contemporary drug-making practices—the so-called Hatch-Waxman Act and related regulations.

Overview of Hatch-Waxman

The Hatch-Waxman Act (Hatch-Waxman) is the popular name for the Drug Price Competition and Patent Term Restoration Act of 1984.[6] Hatch-Waxman and related legislation established a broad array of regulations governing how the pioneer pharmaceutical industry interacts with the generic pharmaceutical industry. Though frequently criticized and challenged, the act has proven remarkably durable.

Hatch-Waxman has its origins in changes made to the drug approval process in the early 1960s. Prior to 1962, drugs were approved for safety only. In 1962, amendments to the Federal Food, Drug, and Cosmetic Act (FDCA) added efficacy as an approval requirement, thereby creating stricter FDA controls and increased approval times. Average total drug development time went from 8.1 years in the 1960s, to 11.6 years in the 1970s, to ~14.2 years in the 1980s and 1990s.[7] Since 1980, the average number of clinical trials conducted prior to filing a new drug application (NDA) has more than doubled, and the number of patients in clinical trials has tripled.[8]

Although the safety and efficacy approval requirements meant a shorter duration of effective patent protection, they also meant generics could not enter the market without repeating the safety and effectiveness studies. Accordingly, some urged that the interests of the public in obtaining lower-cost drugs as soon as possible mandated policies to promote competition from generics.[9] Beset on all sides, Congress fashioned an intricate compromise in 1984. In passing Hatch-Waxman, Congress balanced, on the one hand, the pioneer drug makers' IP rights, which had been eroded by the increasingly burdensome and lengthy FDA regulatory process, against, on the other hand, the need for an expedited pathway for generic drug approval.

Though straightforward in principle, Hatch-Waxman operates through a series of regulatory tradeoffs that can seem complex. We review here the basic operation of Hatch-Waxman and these tradeoffs.

Approval Process

Under Hatch-Waxman, there are 3 possible avenues for the approval and marketing of drug products: a full, formal process; a more streamlined process that allows an applicant to rely partially on existing safety and efficacy data; and a route designed to allow "copycat" drugs to be rapidly approved.[10]

The full, formal process for approving a new drug requires submission of an NDA and reports of investigations demonstrating a drug's safety and effectiveness.[11] The applicant must also provide patent numbers and expiration dates of any patent claiming the drug or a method of using the drug.[11] After an NDA has been approved, the applicant must confirm the patent information already submitted and must submit the same information for patents that subsequently issue. These patents are listed in the FDA publication known as the "Orange Book." A second, more streamlined approval process, created by Hatch-Waxman, allows new drug applicants to rely partially on existing data. Under this process, an applicant must still submit reports of investigations of safety and effectiveness but may also rely on information required for approval that comes from studies "not conducted by or for the applicant and for which the applicant has not received a right of reference."[12] This route of approval is termed a "paper NDA" and can be used for a so-called new chemical entity (NCE) or for changes to previously approved drugs (non-NCE). Examples of such modifications include changes in dosage form, strength, or route of administration; substitution of an active ingredient in a combination product; or changes in formulation, dosing regimen, active ingredient, or indication.[12] Patent listings in the Orange Book are also available for paper NDAs. A third, separate but related streamlining process involves abbreviated applications—called abbreviated new drug applications (ANDAs)—designed primarily to allow a generic manufacturer to copy an NDA holder's drug product. The ANDA applicant is required to show that the drug product is the same in active ingredient, route of administration, dosage form, and strength as the product in the full NDA.[13] The ANDA applicant must further show that the drug product is bioequivalent to the NDA product.[13]

Hatch-Waxman Procedures

When filing an ANDA or a paper NDA, a generic manufacturer must certify that its generic drug will not infringe the patent rights of the pioneer manufacturer. There are 4 types of patent certification:

Paragraph I: Patent information on the drug has not been filed.
Paragraph II: The original patent has expired.
Paragraph III: The patent is about to expire and the generic will not enter the market until the date on which the patent will expire.
Paragraph IV: The patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted.[14,15]

Generic manufacturers that file a Paragraph IV certification must notify the holder of the approved NDA on which the drug is based and must notify each patent holder.[16,17] Upon receiving notification, a pioneer patent holder has 45 days in which to initiate a patent infringement suit against the ANDA or paper NDA applicant.[17,18]

If a patent holder initiates a patent infringement suit in response to a Paragraph IV certification within the 45-day period, the FDA cannot approve the ANDA or paper NDA for 30 months, unless the action is resolved in favor of the generic applicant before that time.[17,18] With a 30-month stay, the patent holder is protected for the first 30 months of the proceedings, and the generic applicant is able to enter the market if the suit is resolved before the end of 30 months.

Data Exclusivity

To facilitate the approval of generic products through the ANDA and paper NDA procedures, Hatch-Waxman and related legislation limited the ability of pioneers to have exclusive rights to certain data that demonstrated the safety and effectiveness of the approved drug. Prior to Hatch-Waxman, the pioneer's exclusive use of its safety and effectiveness data was not limited in duration.

Hatch-Waxman provides limited time periods during which pioneers have exclusive use of the safety and effectiveness data for NCE drugs and non-NCE drugs. For an NCE drug, an applicant cannot submit an ANDA or a paper NDA application for a generic version of the drug to the FDA until 5 years after the date of approval of the pioneer NDA, or until 4 years if a Paragraph IV certification was made.[19] For non-NCE drugs, the FDA cannot approve an ANDA or a paper NDA application for a generic version of a non-NCE drug for 3 years after the date of approval of a pioneer NDA.[20]

Patent Term Restoration

One of Hatch-Waxman's stated goals was to provide relief to pioneer drug makers. Patent term restoration provisions in Hatch-Waxman were motivated by the desire to preserve incentives to innovate, for example, by providing compensation for loss of patent life that resulted from the lengthy approval process. These changes, effected by the 1962 amendments, reduced the average effective patent term from 17 to 9 years.

Several types of patents are eligible for patent term restoration. These include patents covering the product, method of using a product, and method of manufacturing a product. Patent term restoration extends the life of a patent by a portion of the amount of time consumed by the regulatory review period. The regulatory review period is the sum of the time spent in the clinical trial period and in FDA review. The regulatory review period is limited to 5 years. Furthermore, the amount of time added back to the life of a patent may be reduced by any period of lack of due diligence (ie, any period during which the drug sponsor was not being diligent in moving toward product approval by making adequate and timely steps in the process of drug development); by half of the time spent in clinical trials; and by any period that would extend the effective patent life beyond 14 years. It should further be noted that only 1 extension is allowed per regulatory review period.

Patent Infringement Exemption

A final aspect of Hatch-Waxman that deserves special mention here is the so-called patent infringement exemption. Section 271(e)(1) of Hatch-Waxman states:

> It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.[5]

This is sometimes termed the "research exemption."

Federal courts have attempted to define the limits of the section 271(e)(1) exemption more precisely. For example, the US Court of Appeals for the Federal Circuit (the Federal Circuit), the federal appellate court with the primary responsibility for patent cases, recently attempted to narrow the exception in light of concerns about research tools[21]—the precursor molecules and other products used by scientists to conduct research and development for pharmaceutical products.[22] However, the US Supreme Court overturned the Federal Circuit decision, ruling that the

> use of patented compounds in preclinical studies is protected under § 271(e)(1) at least as long as there is a reasonable basis to believe that the compound tested could be the subject of an FDA submission and the experiments will produce the types of information relevant to an IND [investigational new drug] or NDA.[23]

The Court went on to state that "reasonable relation" (to the development and submission of any information under the FDCA) should not be understood narrowly: "Though the contours of this provision are not exact in every respect, the statutory text makes clear that it provides a wide berth for the use of patented drugs in activities related to the federal regulatory process."[23]

Related Exclusivities

In addition to data exclusivity, other "exclusivities" have been developed to promote innovation and competition in products for underserved markets. Though not included in Hatch-Waxman, these other exclusivities operate alongside the Hatch-Waxman system.

Orphan Drug Exclusivity

One such additional exclusivity is termed "orphan drug exclusivity." It applies to those vaccines and diagnostic or preventive drugs either designed to affect conditions that afflict a relatively small number of people in the United States, or for which there is no reasonable expectation of the recovery of research and development costs.[24]

To obtain orphan drug designation, the sponsor must follow the procedures outlined in the Orphan Drug Regulations in 21 CFR §316.20, which include submitting a description of the disease or condition for which the drug will be investigated; a description of the drug to be designated, including all relevant data; and documentation that the target disease meets specific criteria.[25] Furthermore, "the approval of an application for orphan designation is based upon the information submitted by the sponsor. A drug that has obtained orphan designation is said to have 'orphan status.'"[26] Sponsors need to follow the "standard regulatory requirements and process for obtaining market approval."[26]

A sponsor of a drug with orphan status enjoys exclusive approval and market exclusivity for the orphan indication of that drug for 7 years following the date of the drug's marketing approval. A sponsor may request orphan drug designation for a previously unapproved drug or for an already marketed drug. More than one sponsor may receive orphan drug designation for the same drug for the same rare disease or condition.

Pediatric Exclusivity

Another specialized exclusivity involves products designed to benefit pediatric populations. Pediatric exclusivity provides an additional 6 months of market exclusivity to an entity that promotes clinical trials of drugs previously approved by the FDA when such drugs are studied in a pediatric population.[27] The additional market exclusivity means that (1) 6 months is added to the period during which the FDA may not accept for filing or approve an abbreviated application that relies on data from a pioneer NDA; (2) 6 months is added to the period during which generic products cannot be approved as a result of the certifications of patent terms required in abbreviated applications (ie, ANDA and paper NDA); and (3) 6 months is added to any orphan drug exclusivity (for products regulated as drugs under FDCA only). Pediatric exclusivity is an add-on to existing marketing exclusivity or patent protection. In general, products with no patent life or exclusivity remaining cannot qualify for pediatric exclusivity.

Business Importance of Patents

The uncertainties associated with the development of pharmaceuticals are many and substantial. Maximizing the certainty that a research-based manufacturer can obtain, enforce, defend, and make full, legitimate use of IP rights is essential to maintaining the cycle of innovation for the benefit of the public health. In the absence of strong IP rights at each stage of the innovation cycle, the promise of pharmaceutical innovation could be lost.

As noted, patents and other forms of IP protection are designed to reward and protect innovation. Predictable IP rights are important throughout the innovation cycle in at least 4 ways. First, strong IP rights in the earliest stages of drug development encourage research-based companies and other researchers to invest in early-stage innovation, a foundation for the development of new treatments and cures.

Second, IP rights extended to final, marketable drug products make further, related innovation possible. Many drug products contain the potential for further innovation, and IP protection of a marketable drug product encourages not only development of that product but further development of related innovations to expand and improve therapies and cures.

Third, IP protection of marketed products gives their manufacturers the opportunity to benefit financially from the potential commercial advantage created by the innovation. This provides the necessary incentive to promote further investment to support the research, development, and refinement needed for future treatments and cures.

Finally, by promoting the innovation needed for the pharmaceutical industry to provide cures and treatments, IP protection plays an integral role in the creation of a pharmaceutical market in which generic companies can compete with basic research companies following the expiration of IP rights.

The interplay of IP rights with the other factors that determine commercial success creates the vigorously competitive

markets for innovation within and between therapeutic categories of pharmaceutical products. In the pharmaceutical industry, IP rights provide the innovator with a time-limited, exclusive right to market a particular medicine once it has been approved by the FDA.

Conclusion

Under the current US system of patent protection and regulatory oversight of competition, we have seen many advances in the fight against disease. The current system is not perfect, however. Our patent approval process can at times fail to recognize genuine novelty and usefulness, and regulations can be misapplied or circumvented.

The promise and problems of pharmaceutical innovation are difficult to reconcile. Economist Patricia Danzon summarizes our current situation well:

> Overall, the relatively unregulated, more competitive structure of the United States market seems to result in relatively high prices for on-patent originator products and relatively high use of new products, but strong generic competition, high generic share and low generic prices once patents expire, and a relatively large share of the total public price that goes to manufacturers rather than to intermediaries. By contrast, more regulated markets have lower originator prices but larger post-patent sales for originators and less generic competition. The United States structure appears more favorable to innovation.[28]

In whatever way the US government chooses to address US pharmaceutical and health care policy, the important interplay of IP rights, regulation, and innovation needs to be addressed if we are to continue to experience the phenomenal advances in medical treatment that physicians and their patients have come to expect.

Acknowledgment

The author acknowledges the valuable assistance of Thomas Van Gilder, MD, JD, MPH, in the preparation of these materials.

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